FACTS, VIEWS & VISION
Issues in Obstetrics, Gynaecology and Reproductive Health
in ObGyn

11th EUROCAT Symposium on Congenital Anomalies

Antwerp – Belgium, 17th June 2011

BOOK of ABSTRACTS

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KEYNOTE PRESENTATIONS

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The future of prenatal diagnosis

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The development of technology as led to major advances in prenatal diagnosis, but the most recent developments mainly in ultrasound have led to minor, let's call it asymptotic, improvements that due to the high cost of these machines can only be of benefit to the happy few. One ought always bear in mind that the widespread use of less sophisticated techniques and machines is of profit to much more women and their babies than high end machines. In this text I will limit myself to congenital malformations, structural, genetic or functional. Our knowledge on functional malformations or the functional impact of structural malformations is minimal from a prenatal point of view. I will not discuss prediction and prevention if intrauterine growth restriction, preeclampsia and preterm delivery and will not comment on multiple pregnancy, I will also only provide a glimpse on prenatal therapy.

What is the ideal world for prenatal diagnosis? One should aim at 100% antenatal detection, this means that we should not just offer screening towards patients but that we should offer diagnostic modalities to all patient from the beginning. We aim to make diagnosis as early as possible in pregnancy, even before conception. Ideally preconception diagnosis in vivo should be reached. This would allow to treat the fetus as a patient antenatally, offer optimal perinatal support and avoid termination of pregnancy. One can wonder whether he perfect baby is our "holy grail", if not even more " the perfect family". Or is this our nightmare?

Different trends can be discerned in today's prenatal diagnosis. These trends are:

- Diagnosis goes from late in pregnancy to early as illustrated from second trimester amniocentesis and ultrasound to first trimester ultrasound and chorion villi biopsy to preimplantation genetic diagnosis?
- Focus more and more on preconception care.
- Prenatal diagnosis moves from invasive to less invasive to non invasive such as illustrated by congenital hemoglobinopathy which first was diagnosed by cordocentesis, afterwards to polymerase chain reaction on DNA in chorion volli or amniocytes and perhaps diagnosis in maternal blood later on.
- A move from screening and risk determination to immediate diagnosis
- From selective examinations in high risk cases to offering as much test as possible to the general population.

Prenatal diagnosis concerns basically imaging and lab testing. Of course both should be integrated.

On the side of imaging one may expect 3 and 4 dimensional ultrasound to deliver ever increasing image quality. But increasing image quality does not mean that the quality of the operators will increase and the clear image that leaves less to our imagination does not necessarily mean that diagnostic capacity is improved is better. We still wait for convincing evidence of superiority of 4D ultrasound, except in a few fields such as the diagnosis and prognosis of facial abnormalities. I do not expect ultrafast magnetic resonance imaging to really add anything in the future, neither do I think that fetoscopy and embryoscopy will offer new possibilities, certainly not for the general population and in the diagnostic setting. Today we see that prenatal ultrasound has moved to the 11 to 13 weeks scan. For some anomalies a 100% detection rate has been described, including acrania or exomphalos. For others just a 50% detection rate is noted, including diaphragmatic hernia or lethal skeletal dysplasia, for major cardiac anomalies 34% detection rate is noted and for such a frequent and obvious malformation as spina bifida the 11 to 13 week ultrasound scan detection rate is only 14% in highly skilled hands. Perhaps by optimal and repetitive training these numbers can be achieved in all of Europe but even after second trimester scanning todays numbers in Europe must make us realize most humbly that only 96% of cases of anencephaly, 83% of cases of gastroschisis and 68% of cases of spina bifida are diagnosed before birth. The problem of early detection of spina bifida is intriguing. Probably only the most severe cases and those associated with other major abnormalities are diagnosed in the first trimester. This can be due to the poor ossification of the fetal spine, the small size of the spine and the maternal habitus in our even increasing epidemic of obesity. Recently detailed examination of the posterior fossa at 11-13 weeks scan looking for called intracranial translucency might improve our detection rate. This has not yet been convincingly demonstrated.

In the years to come the list of new markers of aneuploidy will become ever increasing. After nuchal translucency, the nasal bone, the increased impedance in the ductus venosus, tricuspid regurgitation, facial angle, liver volume and more recently increased hepatic artery blood flow have been added. Probably other markers will be added but they will not change much in the real uptake of aneuploidy. Humbly we must realize that there will always be anomalies that can never be detected such as microcephaly at the 11-13 weeks as this develops only after 30 weeks, agenesis of the corpus callosum before 18 weeks because the corpus callosum is not developed until that age, or postinfectious problems that only appear a few weeks after the infectious insult. Most cases of polycystic kidney disease will escape from our early prenatal diagnostic capacities as these disease only develops later in pregnancy. Some other prenatal problems must be always detectable such as anencephaly and some will be detectable sometimes including spina bifida, facial cleft ore multicystic kidney at 11-13 weeks scan.

What can we improve in today's ultrasound?

The detection rate of heart and skeleton anomalies lags far behind the detection rate for other systems. Probably the routine assessment of complete cardiac outflow in all patients, optimizing training of prenatal ultrasonographists and perhaps telecardiology with STIC (spatiotemporal image correlation) volumes analysed by an expert elsewhere will improve this part of prenatal diagnosis.

In the near future optimalisation of prenatal ultrasound can increase the amount of first trimester diagnosis of structural anomalies. This will need appropriate training of the sonographers, we really have to take more time for the scan and include detailed examination of the fetal heart. Every fetus with an increased nuchaltranslucency should be reviewed by an expert in echocardiography. From the technical point the resolution will still become better. 4D-ultrasound will become ever faster and perhaps high intensity focused ultrasound (HIFU) will allow local necrosis of tumors or the external treatment of twin to twin transfusion syndrome, local delivery of drugs or DNA in microspheres. We will also see ever involving miniaturisation of the devices.

For the lab tests in prenatal diagnosis we can look at maternal serum screening versus fetal material in the maternal circulation.

Actually maternal serum screening is basically screening for Down syndrome (DS). The detection rate is up to 96% for false positive rates between 3 and 5%. Looking at trisomy 18 and 13 the detection rate is only 75% with DS algorithms but if one uses a specific algorithm the detection rate increases to 95% with a false positive rate of only 0.1%. Incidentally other abnormalities can be found due to maternal serum screening, including Triple X, Smith-Lemli-Opitz syndrome or X linked ichtyosis.

For fetal material in maternal circulation we mention fetal cells and cell free fetal DNA or RNA. Fetal cells have been "the method of the future" ever since the eighties and actually it is not to be expected that there will be any news from this front. The fast evolution in genetics will influence our possibilities in prenatal diagnosis. As array-based comparative genomic hybridization will be used by more and more laboratories, single nucleotide polymorphism detection will become available in more and more centers and even DNA sequencing including shot gun or massive sequencing will become daily practice.

This will allow single cell analysis and perhaps we will have to widen our horizon not only to the human genome project but also to the human epigenome project. 5% of the DNA in the maternal circulation is fetal. This is already used almost in routine practice for fetal sexing or fetal Rhesus D determination and is emerging as a method to detect aneuploidy as has been demonstrated for Trisomy 18, it can be used for the detection of the paternal genome for dominant disorder such as Huntington and perhaps in the future complete genome analysis will be possible, notwithstanding the ethic and social consequences of knowing your child's complete genome before birth. Anyhow cell free fetal DNA will allow to determine aneuploidy and a bunch of genetic diseases, thus systematically offering diagnosis instead off screening to all.

Is there still a future for invasive diagnosis?

Probably yes, microarrays on chorion villi provide incredibly more fetal genetic information than classic karyotype and until now still much more than can be expected from the cell free fetal DNA.. It is to expected that in 1% of sample, when performed in a general population will demonstrate significant genetic disease. This results in major problems concerning counseling but it also changes the risk/benefit ratio for the procedure, if at this moment we provide invasive diagnosis for a risk of 1/270 to 1/300 for Down syndrome and balance this with the risk for procedure related fetal loss between 1/500 and 1/100, then of course finding a significant genetic anomaly in 1%, rationally leads to invasive invasive testing for all.

Some other problems will be encountered in the near future because if we go for more screening more "collateral damage" including incidental findings that are difficult to interpret. This results in more anxiety changing prenatal "care" to prenatal "scare". The obesity epidemic might neutralize the high image resolution development of high definition ultrasound. Where do we stand when we can make very complex diagnoses but are unable to counsel on the functional results of even straightforward diagnoses as hydrocephaly diagnosed in the unborn baby? How to accurately interpret a CMV infection, we are very well capable of demonstrating CMV in the amniotic fluid to prove that the baby is infected but with all our technology we are not capable of telling the parents the functional outcome of their baby. The same kind of uncertainty will result from DNA sequencing. What to tell in case of an incidental finding? What to tell if we know that this fetus is programmed to be autistic, if ever such a diagnosis would be possible?

We can expect the almost classic comments from adversaries of prenatal diagnosis.

It will be argued that prenatal diagnosis can be used for eugenic and social purposes such as sex selection, as is the case in India. In Europe this is forbidden by law, not so in the United States. But this seemingly "ethic" argument is in conflict with the generally accepted view that every generation should aim for the next generation to have a better live. Such selections are perhaps against classic Western European ethics but are our ethics superior and fit for the future? Others will argue that we strive to eradicate certain diseases. Indeed we are! We want to eradicate diseases, but not individuals. Nobody wants to eradicate happy people with Down syndrome. But we would like to eradicate people being born with cystic fibrosis or thalassemia or hemophylia. What is wrong with this? Everyone agrees that we strive to eradicate tuberculosis and malaria, polio or any other infectious diseases. Who is against the eradication of cancer?

In conclusion I state that the most nearby future development should be the improvement of the detection rate for cardiac and skeleton anomalies on ultrasound and moving from the second to the third trimester for the detection of

structural anomalies. Probably cell free fetal DNA in the maternal circulation will replace serum screening for chromosome abnormalities resulting in diagnostic instead of screening tests.

The problem stays that we must wonder how we can make all this high tech care available for all and in the same time still respect the free choice of all to use or not to use these tests.

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This is not a classic article nor a classic list of references, I just present in alphabetical order a series of recent publications, mainly in Prenatal Diagnosis that have been inspiring to me.

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Preconception care to improve pregnancy outcome

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Despite major advances in medical care and the relatively high level of prosperity, poor perinatal outcomes continue to be a major problem in highly developed countries such as the Netherlands (1). This has stimulated a paradigm shift in strategies to improve women's health and pregnancy outcomes from a focus on the prenatal period to the preconceptional period (2). This type of care is called Preconception care (PCC). PCC is a set of interventions that aim to identify and modify biomedical, behavioural, and social risks to a woman's health or pregnancy outcome through prevention and management (3). There is sufficient evidence for several components of PCC and therefore this new care should be consistently offered to women in their reproductive years (4-7). Efforts have to be put in intervention methods and strategies to provide effective PCC. In this regard the following aspects need to be taken in to account: 1) a distinction in general and specialised PCC. It must be clear which components of PCC are provided by general practitioners and midwifes and which components are provided by medical specialists like obstetricians and clinical geneticists; 2) protocols should be drawn up to enable to provide care in a uniform manner; 3) professionals providing PCC need to be trained; 4) risk assessment tools need to be developed and standardised; 5) communication tools and strategies need to be developed and adapted to the local situation; 6) municipal public health institutions and schools need to be involved.

In the Netherlands, several pilot studies on *general* individual preconception care provided by midwives, obstetricians and clinical geneticists have been organized. A self-administered Internet questionnaire for preconception risk assessment for the general population (www.zwangerwijzer.nl) was developed in 2004, subsequently validated (8) and appears to be successful. Such information on risk factors can be used by the caregiver in providing preconception care. Depending on the risk factors, the couple may be referred for *specialist* individual preconception care. Regional and national protocols are being developed to guide such chain system of care in low- and high risk populations. A web based instrument (www.preconceptiewijzer.nl), designed for the caregiver, is now being tested, coupling risk factors with protocols for preconception advice.

In 2009 the municipal council Rotterdam and the Erasmus University Medical Centre started a city wide urban perinatal health program to improve perinatal health outcomes (9). Preconception care is a key element of this ten-years program. Highest priority is given to reach out to ethnic minorities and couples with a low socioeconomic status.

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Preconception care for maternal diabetes prevents congenital anomalies

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Molsted-Pedersen described the high incidence of congenital malformation in offspring of women with diabetes in 1964. In 1994, I was a funding member of the Northern Diabetic Pregnancy Survey and we audited diabetic pregnancy outcomes in the Northern Region of England. In our diabetic population the congenital malformation rate was 83/1000 compared to 21.3/1000 for the background population. Six percent of all fetal losses were due to fetal malformation and 2 late neonatal deaths were due to congenital heart malformations (1).

Since then other studies have confirmed the three fold increased risk of congenital anomaly in offspring of diabetic mothers and CEMACH in 2002/03 demonstrated that in England, Wales and Northern Ireland the prevalence of congenital anomaly for offspring of women with diabetes was 48/1000 for Type 1 diabetes and 43/1000 for Type 2 diabetes. There was a 4.2 fold increase in neural tube defects and a 3.4 fold increase in congenital heart disease (2).

Pathogenesis: Congenital malformations occur in the first 6-7 weeks of gestation. Caudal regression occurs at 3 weeks post fertilisation, spina bifida and anencephaly at 4 weeks and transposition and renal abnormalities at 5 weeks. Our data show that maternal diabetes is associated with a fivefold increase in cardiovascular malformation and that transposition of the great vessels [17 fold excess], truncus arteriosus and tricuspid atresia are over represented (3).

Hyperglycaemia during critical periods of morphogenesis is regarded as the major teratogen in diabetic pregnancies although the causative molecular mechanisms are unknown. In the mouse diabetes model there is evidence that maternal diabetes alters expression of developmental genes in the embryo. It is hypothesised that diabetic pregnancy leads to altered expression of molecules that play key roles in patterning and development of embryonic tissue implicating altered transcriptional regulation as a possible pathogenic mechanism. Currently a unique European wide collaboration, the Congenital heart and environment/epidemiological database [CHEART], is focussing on the mechanisms of normal and abnormal heart development leading to congenital heart disease. This study is testing whether genetic variants are associated with cardiovascular malformation and is investigating gene-environment interactions with maternal diabetes using a genome wide association study.

Evidence to support preconception care: Preconception care was first demonstrated to be effective by Kurt Fuhrmann in 1973 (4). He showed a reduction of congenital malformation from 5.5% to 0.8% by the introduction of tight glucose control prior to conception. Several studies have replicated this finding and a meta-analysis of 14 studies of the effect of preconception care showed that lack of preconception care is associated with a 3 fold increase in the risk of major and minor malformations (5).

Implementation of preconception care: What is preconception care? NICE (6) recommends that avoidance of unplanned pregnancies is an essential component of diabetes education for all women of child bearing age and that:

- Pregnancies should be planned and women should be fully informed of the risks associated with diabetic pregnancy.
- Contraception should be continued until good glycaemic control as measured by HbA1c is established.
- All women should take folic acid 5mg/day from preconception till 12 weeks gestation.

So if the evidence is compelling why are all diabetic women not getting preconception care? A survey by CEMACH showed that in England, Wales and Northern Ireland only 17% of units had a preconception clinic (7). Widespread implementation of the delivery of preconception care has been patchy with variable success. Recently the NHS in England has developed a web based information strategy to support commissioners and providers of care and women with diabetes. This national strategy to improve the uptake and delivery of preconception care was launched in March 2011. It remains to be seen how effective this will be.

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- 004 -

Human biomonitoring: prenatal exposure and effects on the newborn

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Animal toxicology studies, human case studies and occupational exposures have documented that exposure to chemicals at high doses may cause toxic effects on the foetus and newborns. It is much more difficult to predict health effects of continuous exposure to low doses of chemicals such as from air pollution, contaminants in food, chemicals in consumer products (1). Human biomonitoring measures concentrations of chemicals and early effects in human tissues and fluids. Its use in population studies has increased the weight of evidence for linking specific environmental exposures to adverse health effects. Some of the effects may be subtle at the individual level, but may become significant at the population level. Exposure of the developing organism is recognized as a particular concern.

Environmental chemicals which are present in the maternal body may reach the developing embryo and foetus. The mother's body acts as a reservoir. Chemicals selectively pass the placenta. To obtain information on early life exposure, chemical concentrations can be measured in different periods: prenatally in maternal tissue or fluids, at birth in cord blood or placenta, after birth in maternal milk. Human biomonitoring of the general population allows to evaluate time trends in exposure to environmental chemicals and allows to identify high exposure groups among the population. The choice for analysis of eg. blood samples or urine samples depends on the chemicals under study. Exposure to persistent lipophilic chemicals (polyhalogenated compounds such as PCBs, HCB, DDE and PBDEs) are preferentially measured in plasma lipids, while non persistent chemicals such as organophosporous pesticides are preferentially measured through urinary chemical/metabolite concentrations (2). Non-invasive sampling methods such as maternal hair, nails, teeth, expired air are under development and may offer interesting opportunities for biomonitoring of the general population

A range of endpoints have been associated with prenatal chemical exposures. The brain seems particularly sensitive to toxic exposures. During brain development, a complex series of steps must be completed in the right sequence and at the right time. Slight decrements in brain function may have serious implications for future social functioning and economic activities, even in the absence of mental retardation or obvious disease. There were several benchmarking studies which have shown that increased prenatal exposure to methylmercury and PCBs in various cohorts with high fish consumption are associated with delay in cognitive, behavioral, sensory and auditory development. In the Faroe Islands birth cohort cord blood mercury levels were unfavorably associated at age 7 years with test scores for attention, language and memory and at ages 14 for verbal and attention scores (3). In a Dutch cohort, cord plasma and breast milk noncoplanar PCB congener levels have also been associated with cognitive deficits in children age 6-7 years. Also susceptibility to infections, effects on onset of asthma and allergies, effects on growth and puberty development have been associated with chemical exposures. Perinatal exposure to endocrine-disrupting chemicals, such as polychlorinated or polybrominated biphenyls or dichlorodiphenyltrichloroethane compounds have shown to affect puberty development and sexual maturation at adolescence, although not all studies are conclusive and sometimes conflicting results are obtained (4).

Recent concerns about globally observed trends in shortened gestational age and decreased birth weight and the related disease burden have introduced the hypotheses that specific chemicals may alter metabolic programming during prenatal exposure. Fetal growth retardation and low birth weight outcome have been recently associated with prenatal biomarkers of chemical exposures. Several studies reported clinically significant decreases in birth weight of 100 to 200 g if lower and higher exposure percentiles are compared. The magnitude of effect is considerably equal or more than that reported for cigarette smoking (~ 55-189 g reduction). Few studies report on post natal increases in BMI in relation to prenatal exposure. 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p' DDE) has been associated with increased BMI.

Biomarkers of exposure can be complemented by analysis of effect biomarkers and susceptibility biomarkers. The effect biomarkers reflect early biological changes in line with the mode of action of the chemicals such as genotoxicity, endocrine disruption, immune changes, oxidative stress. Recently "omics" technology has been introduced in biomonitoring of the general population allowing high throughput analysis of changes in gene expression, or changes in urinary metabolite or protein profiles. This holds promises for elucidating toxicological pathways through which chemicals cause adverse health effects.

Circulating hormone levels in cord blood have been used as biomarkers for prenatal exposure to environmental chemicals which may act upon hormonal pathways. Hormones, their transporters, their receptors on target organs, and their metabolic pathways are possible targets for endocrine disruptors. Several studies have looked at interference of environmental chemicals with the thyroid system and with circulating sex hormones (5). DNA adducts have been measured in placenta and in cord blood lymphocytes in response to air pollution. It is well known that particulate matter and associated metals and polyaromatic hydrocarbons may cause oxidative damage resulting in DNA adducts and in a changed *in utero* environment (6). Changes in the relative distribution of lymphocyte immunophenotypes in cord blood is another effect marker which has been associated with prenatal polyaromatic hydrocarbon (PAH) pollution and may be one of the first signals of the early impact of environmental exposure on the immune pathways (7). Recently an exploratory study identified an epigenetic marker in human umbilical cord white blood cells which was associated with transplacental PAH exposure and with the risk of developing asthma symptoms prior to age 5. Epigenetic changes may provide a mode of action for prenatal induced changes which may become manifest later in life. Recent molecular epidemiological

studies have identified a number of environmental toxicants that cause altered methylation of human repetitive elements or genes.

To conclude: the mother's chemical body burden will be shared with her fetus or neonate, and the child may, in some instances, be exposed to larger doses relative to the body weight. Developmental exposures to environmental chemicals can lead to a wide range of functional deficits which become manifest after birth and may have life- long health impacts. To understand the underlying mechanisms, molecular markers should be introduced in long-term prospective studies, and existing and planned pregnancy or birth cohorts.

Acknowledgement: EU-COPHES ref.244237 European coordination action on human biomonitoring, COnsortium to Perform Human biomonitoring on a European Scale), EU-OBELIX contract: FOOD- ref.227391 Obesogenic endocrine disrupting chemicals: linking prenatal exposure to the development of obesity later in life, Expertise Centre of Environmental health (Ministry of the Flemish Community, Department of Science, Department of Public Health and Department of Environment).

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- 005 -

Swine flu vaccination during pregnancy, follow-up data - preliminary results of the surveillance project of the Berlin institute for clinical teratology and drug risk assessment in pregnancy

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Pregnant women may be at high risk for severe complications as known from some previous influenza pandemics and seasonal influenza resulting in a higher rate of hospital and intensive care unit admission and death. Beside morbidity and mortality, adverse pregnancy outcomes have been reported following previous influenza pandemics, e.g. birth defects, spontaneous abortion, fetal death, and preterm delivery. In 2009, mass vaccination campaigns against the pandemic H1N1v strain had begun in many countries with pregnant women as a priority group, although the safety of the novel vaccines in pregnancy could not be assessed due to the short time of the product development and the fact that pregnant women are excluded from clinical trials.

The Berlin Teratology Information Service (TIS) was commissioned by the Federal Ministry of Health to counsel physicians and pregnant women about influenza A (H1N1)v 2009 vaccination and to register and evaluate pregnancy outcomes. On September 28th, 2009, the surveillance has been started. Subjects have been prospectively enrolled using a structured questionnaire at the first contact during pregnancy. The following information was obtained: brand name of the vaccine, batch number, reported local or systemic adverse effects after vaccination, timing in pregnancy, details on concomitant medication, flu like symptoms, fever, infections and chronic diseases, maternal demographics, and obstetric history. A comparison group (n = 1.636) was recruited during the same time period, i.e. matched for the estimated date of birth consisting of pregnant women who had been counseled during pregnancy about exposures known to be non-teratogenic. Until March 31, 2010, 359 pregnant women were enrolled who met the criteria for the study, i.e. resident in Germany and exposed to influenza A (H1N1)v 2009 vaccine during pregnancy or less than four weeks prior to conception. A follow-up could be initiated in 344/359 cases. By March 15, 2011 follow-up was completed for 317 (92%) pregnancies. 217 of these women were vaccinated with the non-adjuvanted split vaccine CSL H1N1 Pandemic Influenza Vaccine® (CSL Biotherapies), which was exclusively introduced for pregnant women in January, 2010. In contrast, the AS03-adjuvanted split vaccine Pandemrix® (GlaxoSmithKline) was documented in 86/317 cases, what might reflect the uncertainty and public discussions regarding the use of adjuvanted vaccines in pregnancy. Two patients were vaccinated with the MF59-adjuvanted split vaccine Focetria® (Novartis) and for 12 patients product information could not be obtained.

Based on the preliminary evaluation of our data, swine flu vaccination does not seem to be associated with adverse pregnancy outcomes (table 1). So far, the rate of major birth defects, the pattern of anomalies and the frequency of other outcomes including preeclampsia do not indicate substantial teratogenicity or developmental toxicity of the vaccine. However, since the cohort under study is still rather small and most of the patients were vaccinated after the first trimester we cannot rule out a risk. A final conclusion will be drawn after completion of all enrolled cases, comparison with the control group, and statistical analysis of the data.

Table 1. — Pregnancy outcome after (H1N1)v 2009 vaccination.

Pregnancy outcome	Number of cases
FUP completed	317
spontaneous abortion	6 / 317 (including 1 anencephaly)
elective termination of pregnancy	3 / 317 (including 1 trisomy 21)
live births	308 / 317 (312 live born including 4 pairs of twins)
all congenital anomalies *	28 / 314 (8.9%)
major birth defects *	8 / 313 (2.6%)
preeclampsia	10 / 317

* Number of anomalies by the number of live-born children (n = 312) plus pregnancy losses with malformations (n = 2). For calculation of major birth defects chromosomal/genetic abnormalities were excluded.

- 006 -

Grown ups with congenital heart disease

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Congenital heart diseases are the most common birth defects in humans, affecting approximately 0,8% of all live births. The spectrum of defects is broad, ranging from complex defects that result in profound disability and death in infancy to minor defects that are discovered sometimes only later in life in asymptomatic adults. Before the era of congenital heart surgery a half century ago, fewer than 30% of children with serious congenital heart defects survived to become adults. Considerable progress in pediatric cardiac surgery since then has led to a remarkable improvement in the life expectancy and quality of life of patients with congenital heart disease. Advances in surgical techniques, catheter interventions, anesthesia, and intensive care have rendered virtually all forms of congenital heart disease (CHD) treatable, and infant mortality from CHD has dramatically decreased. Currently, approximately 85% of children with CHD are surviving to adulthood.

The number of grown-up patients with congenital heart disease (GUCH) is constantly increasing and will equal the number of children requiring surgery for CHD. Patients with congenital heart disease however require lifelong medical care. As a result of the above mentioned improvements, the challenges of caring for GUCH patients are only now being realized. Specialized centers dealing with the medical and paramedical problems of these patients are required. We need to educate patients and families about the need for lifelong and skilled surveillance and care.

GUCH patients can be 'roughly' divided in 6 groups, each with special needs and attention:

1. Patients with minor cardiac malformations presenting at adult age for first treatment
2. Patients presenting for correction as adults because they are either naturally balanced or were surgically palliated
3. Patients presenting for expected reoperations after correction in childhood
4. Patients requiring repair of residual defects after correction
5. Patients developing heart failure after correction or palliation of CHD and possibly requiring transplantation
6. Patients developing acquired heart disease in addition to CHD

The grown-up congenital heart patient is not simply a larger subject compared to the CHD child subject. The cardiac lesion by itself is not always the major problem for these patients, since issues pertaining the quality of life and psychosocial aspects (disability, insurance, work, sports, ...) often predominate. It is therefore important to design, adapt and optimize the specific needs.

One of these specific problems is that most women with congenital heart disease are now expected to reach childbearing age, and maternal cardiac disease is the major cause of maternal morbidity and mortality. Appropriate pre-pregnancy counselling and management during pregnancy are fundamental components of the care of these patients.

The care for congenital heart disease is a 'long road'...

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- 007 -

Survival of children born with congenital anomalies

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When a child is born with a congenital anomaly, one of the many questions asked by parents of the medical professionals involved in their care is around the long-term health implications for their child. While advances in fetal and neonatal care have improved the prognosis for individuals with certain anomalies such as Down's syndrome and spina bifida, information on long-term survival is still lacking for many important congenital anomalies. Further, the few studies in the published research literature only consider survival to one year of age and for a limited number of conditions. There are also few studies which have examined the influence of a range of fetal and maternal characteristics on survival status.

In this presentation, I will provide an overview of ongoing work on survival and predictors of survival for children born with a range of congenital anomalies. We have used prospectively collected, population-based data on congenital anomalies extracted from the UK Northern Congenital Abnormality Survey (NorCAS) for the study period 1985-2003. The NorCAS surveys the geographically defined area of the North of England (UK) which has a population of about three million and approximately 32,000 births per year. NorCAS is notified of cases from multiple sources. All anomalies are coded according to the WHO International Classification of Disease (ICD) version 10 and categorised into congenital anomaly group, subtype and syndrome according to current EUROCAT guidelines. Importantly, congenital anomalies were classified hierarchically to take into account the influence of co-incident anomalies on survival. Data on congenital anomalies were matched to three high quality sources of death information: the Northern Perinatal Mortality Survey, a population based survey of all perinatal and infant deaths in the North of England; death registrations from the UK Office for National Statistics; and local hospital mortality records, to determine the survival status of liveborn children. Cases that could not be traced by any of these methods were excluded from the analysis.

Survival status was available for 99•0% of the total sample. 20-year survival was 85•5% (95% CI 84•8-86•3) in individuals born with at least one congenital anomaly and year of birth was a highly significant predictor of survival. As expected, survival varied between subtypes within the same congenital anomaly group; for example, 20-year survival of individuals born with spina bifida with hydrocephalus was lower than that for individuals with spina bifida without hydrocephalus.

This study provides robust estimates of survival for a range of congenital anomaly subtypes, many of which have not been reported previously. It has also demonstrated the importance of presenting survival data for congenital anomalies by subtype because of the high heterogeneity within congenital anomaly groups. This data provides prognostic information to parents and health professionals, and will help to guide commissioning not only for the future health care needs but also the educational and social care requirements of affected individuals and their families. Further long-term studies are needed from other regions and countries to provide good quality data on survival and to further understand the factors that influence survival.

- 008 -

Therapy protocol and outcome of schisis patients in Antwerp

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Our treatment strategy for cleft lip and palate, which is a multi-step one, is discussed in detail. The timing and the used technique in different treatment steps are of crucial importance to enhance the functional and aesthetic results. The first step in the reconstruction of a complete cleft lip & palate is the lip-adhesion combined with presurgical orthopedic, using a molding plate. This is performed at 3 months of age.

A modified Rotation-Advance technique of lip repair together with a primary correction of the nasal tip deformity is performed 3 months later.

The technique of cleft lip and nose repair is presented in detail, as how the cupids bow is rotated down and the secondary defect is filled. Reconstruction of the white roll and the wet line are discussed. Advancement of the lateral segment without the incision around the base of the ala (conventional Millard) is our method of choice.

The primary nasal repair is essential. The depressed and displaced alar cartilage must be repositioned in an anatomical position at the time of the primary lip repair.

The mid long term esthetic results are presented and discussed in detail.

At nine month of age a modified Furlow double opposing Z-plasty is performed to reconstruct the soft palate. The width of the hard palate cleft decreases significantly after the closure of the soft palate. We have been reconstructing the hard palate at the age of 18 to 24 months.

A secondary bone grafting is performed at the age of 6 to 9. The timing of maxillary expansion, before or after alveolar bone grafting is discussed.

The secondary correction of the lip and/or nasal tip are usually performed at the age of 5 to 6. Further the timing of orthodontic treatment, transversal and/or sagital distraction osteogenesis, and eventual orthodognathic surgery in cases with growth deficiencies are discussed.

ORAL PRESENTATIONS

- 009 -

Preconceptional or prenatal Fragile X syndrome screening: 19 years experience in a Belgian Center for Human Genetics

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Fragile X syndrome is one of the most frequent cause of inherited mental retardation. The high frequency of this disease might justify the prenatal or preconceptional screening of women but the question remains controversial. We present here the results of our 19 years experience in this analysis.

Prenatal or preconceptional screening was performed on request of clinicians, mainly geneticists and gynaecologists, for women with no known family history of fragile X syndrome. On a total of 14654 women, a full mutation (more than 200 repeats) was found in one patient and a premutation (55-199 repeats) in 78 patients (1/185).

Genetic counselling was recommended to all premutated women: results were explained to the patients, familial screening was performed and enables the identification of other premutation carriers and availability of prenatal diagnosis was discussed. On a total of 52 foetus from 39 different women, the premutated allele was transmitted 24 times. In 19 cases, mothers had expansion below 70 repeats and the inherited premutation in the foetus ranged from -3 to +12 repeats compared to the mother's premutation. In 5 cases, the mother's expansion was over 70 repeats. In 4 males, the transmission resulted in 3 full mutations and 1 mosaïcism for full mutation and premutation and , in one female, in an unmethylated expansion of about 200 repeats. Pregnancy was terminated in the 4 affected males. This confirms that alleles over 70 repeats are at high risk of expansion to full mutations when transmitted. Such alleles concerned 21 of the 78 premutated women which means 1/697 women of an unselected population.

The debate on the eventuality of wide-scale fragile X syndrome screening in childbearing age women is still tricky. Some publications show interesting data at epidemiological, ethical, or economical points of view. In addition with those different studies, our results could be useful to discuss the interest of such a screening.

- 010 -

Investigating socioeconomic inequalities, risk of congenital anomaly and infant and neonatal mortality in the East Midlands and South Yorkshire Region of the UK

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Objective: To investigate the effect of socioeconomic inequalities on congenital anomaly occurrence and pregnancy outcome, and assess their impact on the widening deprivation gap in infant and neonatal mortality in the UK.

Methods: Population based study of 646749 births in the East Midlands and South Yorkshire 1998-2008. Outcome measures were time trends in socioeconomic variation in the risk of anomaly, time of detection, pregnancy outcome and live birth prevalence. Deprivation measured using the UK index of multiple deprivation 2004.

Results: Non-chromosomal anomaly rates increased significantly with deprivation. Fetuses from the most deprived area had a 54% higher risk compared with the least deprived (95% CI (1.27,1.85). Although antenatal detection rates were similar, rates of termination were lower in the most deprived areas (62%) compared with the least deprived (77%) (RR 0.81 (0.63,1.03)). Consequently, livebirths with a non-chromosomal anomaly were 92% higher (95%CI (1.39,2.67).

Chromosomal anomalies significantly decreased with increasing deprivation (RR 0.54 (0.46,0.63)) due to maternal age (adjusted RR 0.99 (0.85,1.15)). Antenatal detection rates were lower in more deprived areas (RR (0.81 (0.67, 0.97)) with pregnancies less likely to end in termination (RR 0.78 (0.64,0.97)). After adjusting for maternal age, women from the most deprived areas were at 87% increased risk of a livebirth with a chromosomal anomaly (95%CI (1.45,2.40)).

Conclusions: The increase in non-chromosomal congenital anomalies over time, small decreases in rates of termination and socioeconomic variation in pregnancy outcome has resulted in widening, rather than narrowing, the deprivation gap of live born infants with a congenital anomaly.

- 011 -

Validity and reliability of maternal recall of prescription drug use during pregnancy

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In case-control studies that assess associations between drug use and birth defects, detailed information on the type of drug and the timing of use is essential to prevent information bias. However, data on the accuracy of recall of drug use during pregnancy are scarce. Therefore, we validated a self-administered questionnaire by comparing it to pharmacy data which were checked for compliance by maternal interviews. Sensitivity, specificity, levels of agreement, and kappa statistics were calculated to quantify the validity and reliability of the questionnaire for any prescription drug use, groups of drugs, and individual drugs. In addition, we determined whether maternal characteristics influenced the reliability of the questionnaire. A total of 560 women were included. The sensitivity of the questionnaire for any prescription drug use was 57%, ranged between 12% (corticosteroids) and 83% (antihypertensives and thyroid therapy) for drug groups, and between 0% (naproxen) and 73% (salbutamol) for individual drugs. Overall, specificity was high (93-100%). The sensitivity of the questionnaire for prescription drug use during the first 4 months of pregnancy was generally comparable or better than the sensitivity in the complete pregnancy period. Smoking during pregnancy and completing the questionnaire > 1 year after delivery decreased maternal recall of prescription drug use. In conclusion, the validity of maternal recall of prescription drug use during pregnancy is generally moderate to poor. As reliability also differed according to some maternal characteristics, future retrospective studies on the teratogenic risk of drug use may need additional sources of data next to self-reported methods.

- 012 -

Impact of maternal obesity on neural tube defects and cardiovascular anomalies: absolute risk and temporal trends

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Objectives: To derive estimates of the absolute and attributable risks of neural tube defects and cardiovascular anomalies for obese women in England, and predict changes in prevalence resulting from trends in BMI.

Methods: The BMI profile of the maternal population of England and of the prevalence of each outcome were obtained from nationally representative sources. Trends in BMI were modelled by logistic regression. Risk ratios for neural tube defect and cardiovascular anomaly were derived from a recent systematic review. Absolute risks, attributable risks, and future prevalence were estimated.

Results: The estimated absolute risks of a neural tube defect or cardiovascular anomaly for an obese (BMI ≥ 30 kg/m2) pregnant woman in England are 19 (95% confidence interval: 1.6-2.2) and 75 (66-84) per 10,000 births respectively, compared to 10 (9.5-11.4) and 60 (67-63) per 10,000 births respectively for women of recommended BMI (25-29 kg/m2). An estimated 9.8% (5.6-14.1) of neural tube defects and 3.0% (0.5-5.4) of cardiovascular anomalies in England are attributable to maternal obesity.

If maternal BMI trends continue, 24.0% (22.1-25.9) of the maternal population of England will be obese by 2020. This is predicted to result in increases of 6.5% and 4.3% respectively in the prevalences of neural tube defects and cardiovascular anomalies compared with the prevalence in 2010.

Conclusion: This study provides estimates of the individual risk and population burden of neural tube defects and cardiovascular anomalies in England resulting from maternal obesity. The results have implications for public health planning and for providing information to obese women about their pregnancy-related risks.

- 013 -

Risk factors for anorectal malformations using data of 17 EUROCAT registries

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Objective: The etiology of congenital anorectal malformations (ARM) is still largely unknown. We aimed to identify risk factors for ARM using EUROCAT.

Method: We performed a case-control study based on data from 17 EUROCAT congenital malformations registries between 1980 and 2008. Registers included livebirths, stillbirths and terminations of pregnancy following prenatal diagnosis. Cases were 1,393 children with ARM without a syndrome or genetic defect, of whom 631 were isolated, 629 had one or more other defects, and 133 had the VACTERL (Vertebral, Anal, Cardiac, Tracheo-Esophagus, Renal, and Limb)-association. Controls were 19,876 children with a syndrome or known genetic defect. Preliminary analyses were performed using registered information on maternal age, assisted conception, and multiple pregnancies.

Results: Mean age of case mothers (28.9 years) was lower than that of control mothers (33.1 years). Assisted conception, adjusted for maternal age, increased the risk of having a child with ARM (OR = 1.66; 95%CI: 1.21-2.27). No association was found between assisted conception and isolated ARM (OR = 1.14; 95%CI: 0.66-1.98), whereas assisted conception increased the risk of ARM with other defects (OR = 1.85; 95%CI: 1.20-2.85) and VACTERL (OR = 2.88; 95%CI: 1.42-5.84). ARM was also associated with being a twin or triplet (OR = 1.76; 95%CI: 1.18-2.63), after adjustment for maternal age and assisted conception. Results were comparable when the analyses were limited to only livebirths.

Conclusion: These preliminary results demonstrate associations between ARM and assisted conception and multiple pregnancy. More thorough and extended analyses may provide additional interesting findings with regard to risk factors for ARM.

- 014 -

Survey of children with Down's syndrome seen in the Antwerp University Hospital Down team

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Objective: To describe health problems and future needs of children with Down's syndrome seen in the Antwerp University Hospital Down team.

Method: Retrospective review of medical records of children seen between 01-01-2008 and 31-03-2011.

Results: 111 children, 62 boys and 49 girls, age range 0-20 years, were registered. 97% had a free trisomy 21, 1% a Robertsonian translocation, 2% a mosaic form.

49.5% had a congenital heart defect, 2.7% a congenital gastro-intestinal defect, 1.8% congenital cataract. Furthermore there were multiple acquired problems: thyroid dysfunction in 30.6%, gastrointestinal problems in 10.8%, hearing loss in 45%, vision problems in 43.2%, obstructive sleep apnea in 15.3%, stomatologic problems in 7.2%, epilepsy in 6.3%, overweight in 3.6%, orthopedic problems in 4.5%. Feeding difficulties were found in 45% of the children < 3 years. Need for professional early intervention in developmental, psychological and social issues was identified.

Conclusion: Children with Down's syndrome have multiple, complicated and specific health problems requiring a multidisciplinary approach. Early recognition, treatment and prevention of medical health problems is an essential contribution to intellectual development, social interaction and as much autonomy as possible. The medical aspects of care are covered by our team but there is a great need for early intervention in other domains to get full benefit of our efforts.

- 015 -

Congenital anomalies in multiple births in Europe: risk and pregnancy outcomes

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The increase in multiple births across Europe is due to the increasing use of assisted reproductive therapies (ART), and to increasing maternal age. Where foetuses from multiple pregnancies are affected by congenital anomaly; this may affect prenatal diagnosis and outcome. This paper aims to assess risk of congenital anomaly in multiple births, and differences in prenatal diagnosis and pregnancy outcome in affected multiple pregnancies.

Data from EUROCAT population based congenital anomaly registries in 14 European countries, representing over 3.3 million births 2000-2007 were analysed, including 91,000 congenital anomaly cases Registry specific population births data for singleton and multiple deliveries were also obtained.

The population multiple birth rate was approximately 3%. The relative risk of non-chromosomal congenital anomaly in multiple births relative to singletons was 1.39 (95%CI 1.35-1.44), and for chromosomal anomalies 0.65 (0.56-0.74). In approximately 10% of affected twin pairs, both babies are malformed, but not necessarily the same malformation. While congenital anomalies in multiple births are as likely to be diagnosed prenatally, they are less likely than singletons to result in termination, but more likely to result in stillbirth. While multiple births are slightly more likely to be live born there is no difference in early neonatal death rates.

The excess risk of non-chromosomal congenital anomaly in multiple births may result from risk associated to twinning as well as risk associated with ART. Policies of single embryo transfer should lead to lowering of the rate of multiple births, but may simply transfer ART-related congenital anomaly risk to singletons.

POSTER PRESENTATIONS

- 016 -

Epidemiological analysis of a consecutive series of 2,021 terminations of pregnancy due to congenital anomalies, registered by ecemc in Spain

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Objective: Terminations of pregnancy (ToP) after the detection of congenital anomalies (CA) are continuously increasing, and represent an important health issue in the prenatal care field. Our aim was to epidemiologically analyze the series of consecutive ToP registered by ECEMC (Spanish Collaborative Study of Congenital Malformations), in order to establish their characteristics and obtain some clues for prevention.

Method: Data from ECEMC for 1995-2008, in 41 participating hospitals, were analyzed. ECEMC surveyed 1,084,226 consecutive newborn infants (13,019 with CA), and 2,021 ToP with CA. We studied the time distribution of ToP, clinical presentation of their defects, affected body systems, etiological distribution, maternal age, maternal nativity, and comparisons with data for newborn infants.

Results: Percentage of ToP, with respect to total cases, has significantly increased along the time. Among ToP, 39.0% presented isolated defects, 13.9% had multiple defects and 47.1% had different syndromes, being this distribution significantly different from that in newborn infants with CA. There were also differences regarding affected body systems, etiologic distribution, and maternal age. The percentage of immigrant mothers was not different. The comparison of our frequencies for some defects, with those registered by other EUROCAT members will be shown.

Conclusion: Some variables (such as maternal age) to which a special attention should be paid in preconception care were identified. Research and prevention require gathering complete clinical data in ToP, details on family and prenatal history, and biological samples for genetic studies.

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- 017 -

Outcomes following Prenatal Diagnosis of Cystic Hygroma: East Midlands and South Yorkshire Congenital Anomalies Register (EMSYCAR) 2000-2009

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Objective: Outcomes following the antenatal detection of a cystic hygroma are reported as poor, but since most relevant studies originate from tertiary referral centres they may not, therefore, reflect the true overall outcomes from these pregnancies. An early investigation from EMSYCAR 1997-99 suggested a 'normal' outcome for < 10% of affected pregnancies1; more recent data suggest this might require upwards revision.

Method: All cases of cystic hygroma reported to EMSYCAR 2000 to 2009 were identified. Pregnancy outcomes and confirmation of anomaly details following delivery were collected as part of routine data follow-up for registry cases.

Results: Over the ten year period there were 653,687 births and 498 antenatally diagnosed cases of cystic hygroma, a population prevalence of 1:1313 births (95% CI: 1:1202 to 1:1436). Of these, 285 (57.2%) were TOPs, of which nearly two thirds (n = 179, 62.8%) were known to have an abnormal karyotype, and 48 (16.8%) had further anomalies. 58 (20.4%) were isolated cases of cystic hygroma. Median gestation at TOP was 13 weeks (range 11 to 29) with 258/285 (90%) occurring < 20 weeks - before any spontaneous regression of the hygroma, noted in other studies, might have occurred.

However, 213 (42.8%) of the antenatally diagnosed cases opted to continue the pregnancy, with 90 (42%) resulting in a livebirth where the cystic hygroma had resolved and there were no reported anomalies.

Conclusion: Parental counselling may require revision in view of these improved outcomes and the real possibility of spontaneous regression of early diagnosed cases of cystic hygroma.

Reference:

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- 018 -

2009 H1N1 influenza vaccines in pregnant women: A survey in South west France

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In 2009, during A (H1N1)v pandemia, French Health authorities recommend influenza immunisation for pregnant women because of their higher risk of serious influenza outcomes. Thus, the non adjuvanted inactivated influenza vaccine Panenza® has been administered to French women from the second trimester of pregnancy. Several studies suggest that inactivated seasonal influenza vaccines are safe during pregnancy but there are few data about effects of new A(H1N1) vaccines (new antigen) on pregnant women.

Objective: The aim of the present prospective study was to describe pregnancy outcomes among women vaccinated with non adjuvanted influenza vaccine in South Western France.

Methods: from November 2009 to February 2010, volunteered pregnant women who have been vaccinated against A(H1N1)influenza in vaccination centres or maternity-hospitals have been included.

Results: 569 pregnant women have been followed up until delivery. Compared to general population, the risks of maternal pathologies, malformations, or neonatal pathologies were not statistically different.

Conclusion: This study does not allow to detect any safety signal of concern on the effects of the vaccine on pregnancy outcomes; The present survey is included in a larger study performed by several French Pharmacovigilance centers, Pregvaxgrip, which will allow to further assess safety of the A (H1N1)v vaccine.

- 019 -

Pregnancy outcome and prenatal diagnosis of sex chromosome abnormalities in Strasbourg, France, 1995-2006

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Objective: To review the circumstances of diagnosis and the prenatal outcome of the most frequent sex chromosome abnormalities, and to analyse the factors influencing the parental decision to terminate or not the pregnancy.

Method: A retrospective study was carried out among data of the population-based Registry of Congenital Malformations of Alsace (department of Bas-Rhin) in France between 1995 and 2006.

Results: 108 cases of sex chromosomal abnormalities were recorded, including 66 cases of Turner Syndrome, 17 cases of Klinefelter syndrome, 15 cases of Triple X syndrome and 4 cases of 47,XYY syndrome.

Concerning Turner syndrome, 64 of the 66 cases were prenatally diagnosed and 42 pregnancies were terminated. These 64 cases were divided in 17 cases with good fetal prognosis, and 47 severe cases associated with fetal malformations or Bonnevie-Ulrich syndrome. Among the 17 pregnancies with good fetal prognosis, 8 (47%) were terminated. Klinefelter syndrome and Triple X syndrome were all prenatally diagnosed, mostly by systematic sonographic and/or biological screening. Medical abortion was recorded in 53% (9/17) of Klinefelter syndrome, and in 13% (2/15) of triple X syndrome. Concerning XYY syndrome, 3 were prenatally diagnosed: the three pregnancies were continued.

Discussion: This study confirms a high rate of termination of pregnancy following prenatal diagnosis of sex chromosome abnormalities. Nevertheless, the rates are highly variable according the type of the chromosome abnormality, the circumstances of the diagnosis and the medical management of the pregnancy.

- 020 -

Changes in Congenital Anomalies Caused Mortality in Hungary between 1980 And 2006

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Objective: Depending of lethality, the mortality statistics can describe the public health importance of a disease in an approximative manner. The more serious the illness the more informative the mortality statistics, and they are more useful to describe the overall effectiveness of control. The aim of our study was to describe the long term changes in congenital anomalies (CA) mortality and to evaluate reliability of mortality indicators.

Methods: The usual death certification based mortality data was provided by Central Statistical Office. CA had been defined according to the Spanish REpIER classification. We analyzed 47 diseases and 11022 cases from the period of 1980 to 2006 by the usual mortality indicators.

Results: The CA caused standardized mortality decreased from 6.28/million to 4.35/million. The change ICD9 to ICD10 in 1996 did not caused variation in the registered mortality. But the introduction of automatic coding for cause of death increased significantly (by 39%) the registered mortality. The proportion of deaths during 1st year of life decreased from the initial 61.5% to 14.7% and the mean age of mortality increased from 4.76 to 24.94. Early in the 1980's detected 40780 potential life-years lost decreased to 14186 by 2006.

Conclusion: Beside the overall decrease of the mortality burden caused by CAs, remarkable differences between CA groups have been described. The observed trends reflect significant advance in control for some CAs, on the other hand CAs with highly unmet needs have been identified as well.

- 021 -

Quality of life in children and adults with congenital gastro-intestinal anomalies: a systematic review

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Objective: To review studies reporting quality of life (QoL) in children and adults born with congenital gastro-intestinal anomalies requiring neonatal surgery.

Method: Literature search, development of the research protocol and data extraction were performed according to standard systematic review methodology. The review was restricted to studies published in English from 1990 to 2010, using validated instruments for assessment of QoL in children and adults born with congenital diaphragmatic hernia, oesophageal atresia or abdominal wall defects.

Results: From 81 papers identified by the comprehensive literature search, 49 were excluded based on abstract review. Thirty two papers were reviewed independently by two reviewers; 18 (nine in children/adolescents; nine in adults) met the inclusion criteria and were included. All studies measured health-related QoL, none measured subjective wellbeing. Instruments used to assess health-related QoL in children varied considerably, while there was more consistency in adults, most studies used SF-36. Many studies had major methodological weaknesses, e.g. single institution, retrospective cohorts, low sample size, and/or low follow up rates. There was substantial age variation (children 1-15 y, adults 16-58 y). Higher quality papers were from Northern Europe (Netherlands, Finland, Norway). Data from the included studies suggest that QoL of children with these congenital anomalies changes during the life-course and, by adulthood, is comparable with that of the general population.

Conclusion: The reviewed studies consider health status and functioning as a major determinant of QoL. Current concepts of QoL suggest this may be misleading. Further studies need to include age-adjusted, validated instruments to measure QoL throughout the life-course.

- 022 -

Congenital hemangioma, rapid involuting or not?

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Objective: Recognition of uncommon congenital hemangiomas and awareness that its subtypes show different outcomes.

Method: We report the case of a full-term neonate who presented with a large vascular tumor on the right upper leg at birth. Prenatal ultrasound screening failed to detect this tumor. On physical examination, it was difficult to determine the hemodynamic effect of this possibly fast growing tumor. The boy was transferred to a neonatal intensive care unit, where hemodynamic evaluation showed no signs of circulatory decompensation. Doppler ultrasound detected a mass with pronounced venous flow and some arterialization, consistent with a congenital hemangioma. Ultrasound screening of the abdomen did not reveal any other hemangiomas. A conservative approach towards treatment and further evaluation was chosen.

Results: Congenital vascular tumors pose a diagnostic challenge in neonates and recognition of the clinical features and characteristic imaging, can allow a fast assessment of complications and management. In infancy, hemangiomas are the most common vascular tumors. They are not present at birth, go on to proliferate and then involute, whereas uncommon congenital hemangiomas are mature at birth. Congenital hemangiomas can also be classified as rapidly involuting (RICH) or non-involuting (NICH). The outcome of these subtypes, is different from each other. NICH never involutes, demonstrates proportional growth and require excision. The majority of RICH will involute by 12 months of age.

Conclusion: Prenatal identification and imaging can provide insight to the diagnosis of a congenital vascular tumor, which is important for postnatal assessment and management. Congenital hemangiomas can be divided in 2 subtypes, NICH and RICH, with respectively different outcomes.

- 023 -

An unfortunate coincidence...

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Background: Pierson syndrome (PS) is an autosomal recessive disorder characterized by congenital nephrotic syndrome and ophthalmologic anomalies. Cystic fibrosis (CF) is an unrelated genetic disorder with similar inheritance pattern.

Case description: A neonate was transferred to the hospital because of hypotonia and abdominal distention. Renal function was severely impaired and urine analysis showed marked proteinuria. Ophtalmologic examination showed microcoria. This constellation of symptoms led us to suspect the diagnosis of PS. Peritoneal dialysis was started, but unfortunately, the baby died at the age of 5 weeks. Autopsy revealed focal segmental glomerulosclerosis . The diagnosis of PS was genetically confirmed and parents were counseled.

During a second pregnancy, chorion villi sampling showed that the fetus was also affected and the pregnancy was terminated. In this process, parents were offered screening for carriership of CF mutations. As a surprise, they turned out to be both carriers for this condition as well. Because their first child experienced respiratory and gastro-intestinal problems in the neonatal period, genetic analysis of the CF gene was performed and the child turned out to be affected.

Genetics: The affected child was compound heterozygous for two mutations in the LAMB2-gene: the c.529_537delTATTTCTCC mutation in exon 5 and the c.3595C > T mutation in exon 24 . For CF, the child was also compound heterozygous: c.1521_1523delCTT (p.F508del) and c.3752G > A (p.S1251N) were the two mutations identified in the CFTR gene. Both parents are heterozygote carriers for one of the two mutations in each gene. There is no evidence for consanguinity in the parents since for both genes no homozygosity was observed in the affected child.

Conclusion: The coincidence of two recessive conditions in one child is exceptional, certainly when there is no evidence for consanguinity in the parents. This case also illustrates that the co-occurrence of two conditions may sometimes complicate the diagnostic work-up in a child presenting with rare anomalies in the neonatal period.

- 024 -

The Effect of Prenatal Screening using Combined Ultrasound and Biochemical Analysis on Termination Rates and Rates of Down Syndrome in Newborns

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Objective: Evaluation of the Swedish prenatal screening programs on the termination rates and the rates of Down Syndrome (DS) in newborns. In 2009, 13 of the 21 Swedish counties performed free combined ultrasound and biochemical analysis (CUB) in early pregnancy, usually only offered to women 35 years of age or more.

Methods: Infants or aborted fetuses with trisomy 21 were identified using the Swedish Register on Congenital Malformations (RCM). Information from the Swedish Medical Birth Register was used to gather background information. The expected number of DS cases was estimated by applying the equation proposed by Lindsten *et al.* (1981) on population data.

Results: The expected number of DS was almost identical to the sum of the number of reported infants and aborted foetuses with DS, suggesting a close to complete reporting of DS to the RCM. The rate of newborn children with DS was constant over time since 1978, despite the fact that the mean maternal age increased considerably. Among born infants, the rate of DS in counties where CUB was used was almost identical to the corresponding rate in counties without CUB. However, the number of aborted foetuses with trisomy 21 was significantly higher in counties using CUB.

Conclusion: By early detection of chromosomal defects, several terminations were performed to end pregnancies that would have resulted in early miscarriages if no interventions were made.

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Second trimester elevated maternal serum alphafetoprotein and risks of fetal anomalies

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Background and objective: Maternal serum AFP is measured as part of the triple test for screening of Downs syndrome in the second trimester. Elevated levels of MSAFP have been associated with increase risks of neural tube defects NTD and adverse pregnancy outcome.

The purpose of our study was to study the profile of congenital anomalies associated with raised MSAFP.

Materials and methods: The results of all women in Wales with a raised MSAFP between April 2004 and December 2009 with a subsequent congenital anomaly were studied. The data were extracted from the University Hospital of Wales laboratory and the Congenital Anomaly Register for Wales. A profile of fetal anomalies was described.

Results: Over the study period the total number of women who had the MSAFP levels carried out as a part of the triple test were 99,427. Out of them, 1314 (1.3%) women had MSAFP levels at or above 2.2 multiples of the mean. Of these 132 (10%) had one or more congenital anomaly.

15 (12%) had a chromosomal abnormality and 117 (88%) had one or more structural congenital malformations.

The most common fetal abnormality was neural tube defect affecting 42 (3%) of cases screened. This was followed by gastroschisis affecting 34(2.6%) of cases screened. During the same period a total of 285 neural tube defects and 133 cases of gastroschisis were detected. Those identified by a raised MSAFP represents 15% and 25% respectively of total Welsh population with these conditions.

The other relatively common anomaly we found in our series was congenital heart defects effecting 14 (1%) cases with elevated maternal MSAFP. In the same period a total of 2272 cardiac defects were reported. Those with a raised MSAFP represent only 0.6% of the population with a known cardiac anomaly. Limb defects affected 7 (0.5%) cases whose mothers' were screen positive and congenital renal anomalies also affected 7 (0.5%) cases. Those cases with a raised maternal MSAFP represent only 0.5% and 0.7% of the population with a known limb defect or renal anomalies respectively.

Conclusion: This data shows that there is a 10% chance of having a congenital anomaly if the maternal serum alpha protein is elevated. However the anomalies associated with elevated MSAFP represent only a small proportion of the total fetal anomalies diagnosed during the study period. This shows that MSAFP is not a reliable test for the detection of fetal anomalies in Welsh population.

- 026 -

A study of the incidence of congenital malformation and associated risk factors in Saudi population

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Objectives: This prospective study was undertaken: (i) To determine the extent and nature of congenital malformations in babies born in Riyadh Military Hospital, Riyadh, K.S.A. (ii) To identify the risk factors (genetic/environmental) associated with birth defects.

Methods: A total of 5052 babies born in Riyadh Military Hospital between July 1, and December 31, 2010 were included in this study. The diagnosis of malformation was based on:

a. Prenatally: mainly at first ultra sound imaging of mother.
b. At birth by a thorough examination of baby by a neonatologist.
c. Postnatally: at 1 month in a special clinical setup for this purpose.

The identification of associated risk factors was based on parent's detailed history and interviews to determine consanguinity, maternal diseases/infections, previous history of birth defects, use of drugs during first trimester and exposure of parents to teratogens and laboratory studies. The data was stored and analyzed using a modified EUROCAT program.

Results: The analysis of data showed the incidence of malformation was 4% of the babies born in RMH with various types of congenital anomalies, which is significantly higher as compared to the incidence of anomalies reported from Europe (2.8%). The heart anomalies were the leading congenital defects (10.1/1000 pregnancies), followed by urinary malformation (9.3/1000 pregnancies) and CNS abnormalities (4.9/1000 pregnancies).

Conclusion: Our results clearly showed that the pattern and extent of congenital malformation is significantly different as compared to western population. Analysis of risk factors showed that consanguinity had definite association with congenital birth defects. Other suspected risk factors associated with malformations are being analyzed.

- 027 -

EFEMERIS (Evaluation chez la Femme Enceinte des MEdicaments et de leurs RISques), the French prescription database in pregnant women: a 4 year-follow up

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Objective: The main aim of this study is to move towards setting up the first French database of reimbursed drugs prescribed to pregnant women by associating records of the drugs prescribed and delivered during pregnancy until the outcome of these pregnancies.

Method: EFEMERIS database was set up with the data on prescription drugs given to pregnant women recorded by the Caisse Primaire d'Assurance Maladie (CPAM) of Haute-Garonne and the outcomes of these pregnancies obtained from the Protection Maternelle et Infantile (child health certificates) and the Centre de Diagnostic Antenatal (medical pregnancy interruptions). Data collection currently concerns 4 years. Women delivered from July 1st 2004 to June 30th 2008 in Haute-Garonne and registered in the French Health Insurance Service are included into the EFEMERIS database.

Results: EFEMERIS includes 40,355 mother-outcome pairs (newborns or fetus if the pregnancy was stopped). The prevalence rate of congenital anomalies is 2.3%. Pregnant women are prescribed 10.8 ± 7.6 [0-78] different drugs. Among the twenty most frequently prescribed drugs, around half of them are not evaluated in pregnant women (phloroglucinol, dompéridone, diosmine...). Among the drugs for which data is available, some with proven teratogenic or fœtotoxic effects are prescribed and delivered to pregnant patients included in the EFEMERIS database: retinoids, NSAIDs...

Conclusion: EFEMERIS is the first French database of drugs prescribed and dispensed during pregnancy including the outcome of these pregnancies (birth or medical termination of pregnancy). This database would constitute a monitoring centre for the prescription of drugs to pregnant women and would allow evaluating the potential teratogenic risk of drugs.

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Progesterone in pregnancy: a comparative study in EFEMERIS database

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An association between progestin exposure during pregnancy and congenital anomalies (mainly hypospadias) has been reported in three studies. In contrast, other authors could not identify an increased risk.

Objective: The present study investigates potential teratogenic risk of progesterone in pregnancy.

Method: EFEMERIS is a database including prescribed and delivered drugs during pregnancy and outcomes. Women delivered from July 1st 2004 to June 30th 2008 in Haute-Garonne and registered in the French Health Insurance Service were included into EFEMERIS database. We compared pregnancy outcomes and newborn health between women exposed to progesterone during organogenesis and non exposed women.

Results: 1, 519 (3.8%) newborns exposed during organogenesis to progesterone were compared with 38 464 controls (non exposed newborns). The average age of the mothers was 32.6 ± 4.9 years in exposed group and 30.1 ± 5.0 in the control group ($p < 10\text{-}4$). Prematurity rate was higher in the group of newborns exposed to progesterone than in controls (10.9% vs 4.8%, $p < 10\text{-}4$). In the group of newborns whose mother had a prescription of progesterone during organogenesis, 47 (3.1%) had a malformation versus 872 (2.3%) in the control group ($p = 0.04$). Exposed newborns had more nervous system malformations than controls (6.6‰ versus 2.0‰, OR = 3.3 [1.7-6.3]). In contrast, the risk of urinary malformations was similar in the 2 groups (4.6% in exposed group versus 4.8% in controls, $p = 0.9$).

Conclusion: The present study found an association between progesterone prescription during organogenesis and birth defects, i.e. nervous system anomalies.

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Cerebral cavernous malformations (CCM)

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A five year old girl was referred with a history of recurrent falls for six weeks. The falls have always been towards the left side and can happen at least once every day. This was followed by a sudden onset of weakness of the left leg associated with shooting electrical pain across the left leg lasting between 30 seconds to 5 minutes. On general examination she had minor vascular markings at the back of her neck. Other systems examination was normal and neurological examination showed a slight weakness with increased tone in left upper limb and lower limbs with hyper- reflexia. She had a slightly asymmetrical gait with left arm held out. She had investigations in view of the history and neurology findings. Her MRI Head showed right posterior parietal vascular anomaly consistent with a cavernous angioma. She is being conservatively managed and the falls have improved with carbamazepine treatment on suspicion of sensory seizures. Mother did mention that the other sibling has got vascular marking of his hand and complains of recurrent headaches. On examining the other child, he had extensive capillary vascular marking extending over his entire right arm and also in the left thigh. He had MRI head which also confirmed of cavernous angioma.

Mother also has vascular marking at the back of her neck measuring up to 12 cm and the family was referred to the Genetics clinic. Blood samples were sent to Belgium to look for KRIT1, most common gene related to blood vessel malformations that run in families. Discussion

Cerebral cavernous malformations (CCM) are areas of abnormally dilated capillaries within an otherwise normal tissue. The incidence in the general population is roughly 0.5%, and clinical symptoms typically appear between 20 to 30 years of age (1). This disease is characterized by grossly dilated blood vessels with a single layer of endothelium and an absence of neuronal tissue within the lesions. These thinly-walled vessels resemble sinusoidal cavities filled with stagnant blood. Blood vessels in patients with CCM can range from a few millimetres to several centimetres in diameter. Many patients live their whole life without knowing they have a cerebral cavernous malformation. Other patients can have severe symptoms like seizures, headaches, paralysis, bleeding in the brain (cerebral haemorrhage or hemorrhagic stroke) and even death. The nature and severity of the symptoms depend on the lesion's location in the brain. Approximately 70% of these lesions occur in the supratentorial region of the brain; the remaining 30% occur in the infratentorial region. Cavernous angioma can also occur in the spinal cord.

Diagnosis is most commonly made accidentally by routine magnetic resonance imaging (MRI) screening. Sometimes the lesion appearance imaged by MRI may remain inconclusive and might warrant further imaging like cerebral angiogram or magnetic resonance angiogram (MRA). Bleeding is the most important complication and management depends on it. When patients present with recurrent haemorrhage, progressive neurological deterioration, or intractable epilepsy, then treatment in the form of surgery should be considered. The decision to operate on a patient with a cavernous malformation must be made based on the exact location of the lesion and its surgical accessibility. By and large surgery offers an excellent option in terms of complete excision of lesion with stabilization of symptoms. Even seemingly deep- seated lesions can be reached using currently available stereo tactic techniques (2).

Familial forms of CCM occur at four known genetic loci and follows autosomal dominant inheritance3. Mutations in the KRIT1 gene may account for up to 40 percent of all familial cerebral cavernous malformation cases. Cerebral Cavernous Malformations (CCM) are vascular malformations that are mostly located in the central nervous system and occasionally within the skin and retina, which are classified into three types (CCM1, CCM2 and CCM (3)) by being located at different loci on chromosomes (4). The gene for CCM encodes KRIT1 (krev interaction trapped 1) and has been found to bind to ICAP1alpha (integrin cytoplasmic domain associated protein alpha), a beta 1 integrin associated protein (5). The KRIT1 gene (also known as the CCM1 gene) provides instructions for making a protein (KRIT1 protein) that likely plays an important role in the formation of blood vessels, especially capillaries, during the development of an embryo. More than 100 mutations that cause cerebral cavernous malformations have been identified in the KRIT1 gene. Virtually all of these mutations place a premature stop signal in the instructions for making the KRIT1 protein, preventing adequate KRIT1 protein production. Without enough KRIT1 protein, blood vessels do not form properly and cavernous malformations can develop.

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- 030 -

Congenital malformations in children delivered by women employed in agriculture and residing in rural areas

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Several reports suggest that women employed in agriculture who reside in rural areas may be at a higher risk of giving birth to a child with congenital malformations. It is thought in most of these cases congenital malformations stem from exogenous and multi-factorial etiology.

The aim of this observational study is to compare the characteristics of malformations in children being delivered by women residing in rural areas and being employed in agriculture (N = 1,528) with the nature of malformations in children delivered by women employed as white-collar workers and residing in urban areas (N = 1,935). All cases were reported and registered in the Polish Registry of Congenital Malformations during a 10-year period (1998-2008). All pairwise comparisons of categorical characteristics were performed using chi-square test (or Fisher's exact test for less frequent traits).

Compared to the affected children delivered by women living in rural areas and working in agriculture, the cases delivered by women living in urban areas and working as white-collar employees were more frequently affected by isolated hydrocephaly, as well as isolated cleft palate and cleft lip. In contrast, the cases reported from urban areas whose mothers were employed as white-collar workers, were more frequently affected by urinary system defects and chromosomal aberrations distinct from Down Syndrome.

The Project is financed by the Polish Ministry of Health.

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The aim of this study was to analyze the outcome of three flap designs to correct non-syndromic Tessier no. 2 and 3 facial cleft

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Methods: Twenty two patients with non-syndromic Tessier no. 2 and 11 patients with Tessier no. 3 facial cleft that reported to the GSR Craniofacial Institute, Hyderabad, India, from 2003 to 2009 were enrolled in this study. A nasal dorsum rotational flap design was used in 15 patients with Tessier no. 2 and 8 patients with Tessier no. 3 facial cleft. A nasolabial transposition flap design was used in 6 patients with Tessier no. 2 facial cleft. A forehead-eyelid-nasal transposition flap design was used in 1 patient with Tessier no. 2 and 3 patients with Tessier no. 3 facial cleft. Photogrammetric analysis was performed on standardised full face frontal and submental oblique view photographs preoperatively and one year postoperatively to assess nasal symmetry. Ratios between the measurements of the cleft side and the non-cleft side were calculated. A ratio close to one was indicative of good symmetry.

Results: The mean nostril symmetry ratio improved in the nasal dorsum rotation flap group from 0.79 to 0.89. In the nasolabial transposition flap design group the mean nostril symmetry ratio did not improve. The forehead-eyelid-nasal transposition flap group improved from 0.80 to 0.92.

The mean postoperative alar base asymmetry ratio improved in the forehead-eyelid-nasal transposition flap group from 0.71 to 0.93. The mean alar base asymmetry remained practically unchanged for the nasal dorsum rotation flap group (0.90 to 0.90) and for the nasolabial transposition flap group (0.89 to 0.90).

Conclusion: Three different flap designs were used for treating Tessier number 2 and Tessier number 3 facial clefts. The Nasal symmetry outcome was evaluated one year postoperatively using photogrammetric analysis. The dorsal rotation flap improved nostril symmetry but not alar symmetry. The nasolabial flap did not improve nostril or alar symmetry. The forehead nasal rotation flap improved alar and nostril symmetry.

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Prenatal ultrasound diagnosis of oculoauriculovertebral spectrum disorder

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Background: Oculoauriculovertebral spectrum (OAVS) is a complex malformation syndrome that affects structures derived from first and second branchial arches. Associated abnormalities include cardiac, urinary and CNS nervous system defects The purpose of this study was to determine the contribution of routine prenatal ultrasound screening to early diagnosing of OAVS and its possible influence on the pregnancy outcome.

Method: We have used data from the EUROCAT (European Surveillance of Congenital Anomalies) database, a large European network of birth defect registries which use multiple sources and active cases ascertainment. Data were extracted for 1980-2007 period using appropriate ICD9/ICD10/BPA extension and OMIM codes. Of a total of 303 cases of OAVS registered during monitored period, 149 cases had data about prenatal ultrasound examination.

Results: Prenatal ultrasound investigation detected abnormalities in 37/149 (24.8%) fetuses, while in 112 (75.2%) fetuses sonographic examination was normal. Mean gestational age at discovery of an abnormality by prenatal ultrasound was 22.36 ± 5.34 (11-32) weeks. Cephalic abnormalities were found in 29/37 cases (78.3%). The most frequently detected anomalies from the OAVS spectrum were ear (83.7%) and spine (43.24%) malformations. Congenital heart disease was present in 12/37 (32.4%) fetuses and central nervous system and urogenital defects in 27% fetuses each. Out of the 37 prenatally detected fetuses, 14 were terminated at 17-36 gestational weeks, all in presence of severe malformations.

Conclusion: Prenatal ultrasound has evolved in a powerful diagnostic tool. Still, at present it detects only one quarter of OAVS fetuses, mainly those with major anomalies of face, neck and spine.

- 033 -

Awareness, knowledge and use of folic acid among women in Tuscany (Italy)

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Objective: The intake of folic acid (FA) prior the conception and during the early stages of pregnancy plays a key role in preventing neural tube defects (NTDs) and other birth anomalies. To investigate the awareness and knowledge about FA a survey was carried out in Tuscany among childbearing age women.

Method: A questionnaire was administered to 400 women delivering in 9 maternity units in Tuscany from 29th June to 29th September 2010. Women were stratified in three groups: AFA (Appropriate Folic Acid, by use and period), OFA (Other Folic Acid = wrong use or period), NFA (no folic acid).

Results: The mean age of the women was 33.3 ± 4.8 years. Pregnancies were planned by 50.9% of the women. AFA women were 110 (27.5%), OFA 260 (65.0%), NFA 30 (7.5%). Three hundred and eighty-one of the women (95.3%) reported that they had heard about FA: 190 women (49.9%) had heard about FA before pregnancy, while 191 (50.1%) during pregnancy. Among the women who were aware of FA 251 women (65.9%) reported that FA must be taken before the pregnancy, 257 women (67.5%) that it could help to prevent birth defects, and 304 (79.8%) specified its role in preventing NTDs. The main source of information was gynaecologist/obstetrician (338 = 88.7%).

Conclusion: Even if a national recommendation for 0.4 mg/day periconceptional supplementation has been diffused since 2004, in our sample almost all the women surveyed (95.3%) had heard about FA but only one woman out of three had correctly taken FA by time and dose.

- 034 -

A register-based study of bladder exstrophies and epispadias complex: prevalence, associated anomalies, prenatal diagnosis and survival

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Objective: The bladder exstrophy-epispadias complex (BEEC) is the most serious form of abdominal midline malformation. The aim of this study is to describe the prevalence, associated anomalies, prenatal diagnosis and survival of cases of BEEC.

Method: Data were extracted from the Northern Congenital Abnormality Survey (NorCAS) for cases delivered during 1985 to 2008.

Results: A total of 43 cases were notified from 824,368 registered births giving a total prevalence of 5.22 per 100,000 (95%CI 3.77, 7.03). Excluding one twin with cloacal exstrophy, 42 cases occurred in singleton pregnancies. Twenty-nine (69%) cases were isolated and 13 (31%) were associated with other congenital anomalies; 11 (26%) with other structural anomalies and two (4.7%) with chromosomal anomalies. The male to female ratio was 2.2:1 for all singleton cases and 1.4:1 for isolated cases. The total prevalence for BEEC singleton cases was 5.10 per 100,000 registered births (95%CI 3.67, 6.89) and the overall live birth prevalence was 4.63 per 100,000 live births (95%CI 3.28,6.36). For isolated cases of BEEC, the total prevalence was 3.52 per 100,000 births (95%CI 2.36, 5.05) and the live birth prevalence was 3.29 per 100,000 live births (95%CI 2.17, 4.79). The accuracy of prenatal diagnosis was low with only four cases (10%) being detected by routine ultrasound scan prenatally; three with bladder exstrophy and one with cloacal exstrophy. The overall survival of all infants at one year was 95%.

Conclusion: This population-based study demonstrates a prevalence rate similar to other studies, a low prenatal diagnosis rate but a high survival.

- 035 -

Small intestinal atresia in Europe: prevalence and associated anomalies

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Objective: To examine the prevalence of small intestinal atresia (SIA) and its subtypes in Europe and to describe the presence and type of associated anomalies.

Methods: SIA cases delivered during 1990-2006 and notified to 20 European congenital anomaly registers formed this population-based case series. Total prevalence rates for SIA, duodenal atresia and jejunoileal atresia (JIA) were calculated as the number of cases (fetal losses, termination of pregnancy for fetal anomaly, or live birth) per 10,000 total births. 95% confidence intervals (CIs) were derived from the binomial distribution.

Results: 1,133 SIA cases were reported among 5,126,164 registered births. The prevalence per 10,000 births for singleton cases of normal karyotype was 1.6 (95%CI = 1.5-1.7) for SIA, 0.9 (95%CI = 0.8-1.0) for duodenal atresia and 0.7 (95%CI = 0.7-0.8) for JIA. Of 1,044 singleton cases, 215 (20.6%) were associated with chromosomal or genetic syndromes, 200 (19.2%) with duodenal atresia and 15 (1.4%) with JIA ($p < 0.001$, for difference). 173 (16.6%) had Down syndrome, which was associated with 170 (16.3%) duodenal atresia and three JIA cases ($p < 0.001$, for difference). Of the remaining 829 singleton cases with normal karyotype, 221 (26.7%) were associated with other structural anomalies, where 149 (17.9%) and 72 (8.7%) were associated with duodenal atresia and JIA, respectively ($p < 0.001$, for difference). Cardiovascular anomalies were most common, occurring in 85 (10.3%) singleton normal karyotype cases and were more common in duodenal atresia cases than JIA cases (60 (7.2%) and 25(3.0%) respectively; $p = 0.001$).

Conclusion: Chromosomal and structural anomalies were significantly more common in duodenal atresia cases compared to JIA cases.

- 036 -

Does maternal body mass index impact on the antenatal detection of congenital anomalies?

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Objective: Raised maternal body mass index (BMI) is associated with an increased risk of congenital anomaly. This may partly be explained by differences in antenatal detection of anomalies and hence, varied termination rates. This study aimed to investigate the association between maternal BMI and antenatal detection of congenital anomalies in a population-based case-series from Northeast England.

Methods: Data on congenital anomalies occurring in singleton pregnancies booked and delivered in five maternity units in Northeast England during 2003-2005 were linked with data from the Northern Congenital Abnormality Survey. Adjusted odds ratios (aORs) for antenatal detection (of any anomaly) according to maternal BMI were estimated using logistic regression.

Results: 961 congenital anomaly cases were reported among 40,934 pregnancies, a prevalence of 224 (95% confidence interval, CI: 208-237) per 10,000 births. Antenatal detection of any anomaly occurred in 429 (44.6%) cases. The odds of detection significantly decreased with increasing maternal BMI (aOR, per Kg/m2 = 0.97, 95% CI: 0.94-0.99; p = 0.018). However, there was no evidence that termination of pregnancy was associated with maternal BMI (aOR = 0.96, 95% CI: 0.93-1.01; p = 0.08). Overall, 416 (43.4%) cases were associated with cardiovascular anomalies (prevalence: 102 (95% CI: 92-112) per 10,000 births). In 89 (21.4%) of these, an anomaly of the cardiovascular system was detected antenatally, and the odds of detection decreased significantly with increasing maternal BMI (aOR, per Kg/m2 = 0.93, 95% CI: 0.87-0.99; p = 0.02).

Conclusion: Antenatal detection of a congenital anomaly decreases with increasing maternal BMI. This has implications for the scanning and counselling of overweight and obese pregnant women.

- 037 -

Antenatal detection and outcome of pregnancy affected by congenital anomaly in women with pre-gestational diabetes: regional cohort study

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Objective: Women with pre-gestational diabetes (PGDM) are at increased risk of pregnancy affected by a congenital anomaly. UK national guidance recommends enhanced antenatal ultrasound screening for cardiovascular defects. This study compared antenatal detection of congenital anomaly, and outcomes of affected pregnancies, in women with and without PGDM.

Methods: We linked data for 1996-2008 from the Northern Diabetes in Pregnancy and Northern Congenital Abnormality Surveys in the North of England. Antenatal detection of major structural congenital anomaly in singleton pregnancies resulting in miscarriages ≥20 weeks, terminations of pregnancy for congenital anomaly, stillbirths and live births was compared between women with and without PGDM.

Results: There were 120 affected offspring among 1677 pregnancies in women with PGDM (71.6 per 1000), compared to 19.1 per 1000 in women without diabetes (RR 3.8, 95% CI 3.2-4.5). 44 (37%) anomalies in women with PGDM were cardiovascular anomalies, but the risk was increased for all major groups. 51% of all anomalies were detected antenatally in women with PGDM compared with 41% in those without (RR 1.23, 95% CI 1.03-1.47). For cardiovascular anomalies, 32% vs 10% were detected antenatally (RR 3.06, 95% CI 1.96-4.77). Outcome of affected pregnancy was similar in women with and without PGDM: 18% vs 14% resulted in termination of pregnancy and 72% vs 78% were alive at one year. 3% of cardiovascular anomalies resulted in termination; none in women with PGDM.

Conclusion: A higher proportion of anomalies was detected antenatally in women with PGDM, but this did not influence pregnancy outcomes.

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Incidence of congenital cardiopathy in secondary level hospital settings

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A congenital cardiopathy is a type of defect or malformation of the structure of the heart or blood vessels that occurs at the beginning of the pregnancy. It affects 8-10 out of every 1000 children. The level of health care which is provided in hospital settings is very important for early diagnosis.

Objective: This retrospective study set out to estimate the incidence of congenital cardiopathy in newborns in general hospital through period from 2003 to 2009 year. Material and method: Data were collected from medical documentation at postnatal department in Prilep General Hospital. Results: Of the 7956 total number of live births in the period 2003-2009, 25 newborns had some congenital cardiopathy diagnosed postnatally (incidence 3,1/1000).

Conclusion: Improvement of health care is very important for early diagnosis and treatment of congenital cardiopathy. Early prenatal diagnosis and early adequate treatment after birth lead to decreasing the high morbidity and poor prognosis of newborns with this anomaly. A multidisciplinary approach is recommended for defining the aetiology and developing individual treatment strategies.

- 039 -

Prenatal Screening And Diagnosis Of Down Syndrome In Hungary, 2001-2009. Clinical Autdit Of Prenatal Screening Of Down Syndrome

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Objective: To present the time-trend analysis in occurrence of Down syndrome (DS) in Hungary; to evaluate the impact of significant demographic changes in maternal age on DS prevalence; to summarize the effectiveness of prenatal screening (PS) of DS by maternal age-groups and territorial distribution; to compare the results of PS of fetus with DS with the data of EUROCAT's Registers; to present the planning clinical audit of DS.

Method: The population-based large dataset of the Hungarian Congenital Abnormality Registry and Surveillance (HACRS) established in 1970 collects information in cases (live births, stillbirth's babies, affected fetus) with births defects including DS. Active search of unrecorded cases significantly expanded the HCARS database. Demographic data of the Hungarian population at large were obtained from the National Statistical Office.

Results: In the study period (2001-2009) the prevalence of DS was 1.78 per 1,000 births. The rate of mothers older than 35 years increased from 8% to 15%. In 2009, 60,6% of fetus with DS were prenatally identified (in 2001, this rate was 33.3%). The proportion of antenatal diagnosis parallel increased with the maternal age (in 2009: < = 20: 16.7% – > = 35: 73%). There was a significant variability in the efficiency of PS by region.

Conclusion: The prevalence of DS and the efficiency of PS was slightly lower than the values observed in other European countries. PS showed a significant improvement year by year. Clinical audit could help to identify the weak points of screening and the find out the necessity of intervention.

- 040 -

Neural Malformations in Chornobyl Impacted Region of Ukraine

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Background: A report by the WHO/IAEA/UNDP asserted that because of relatively low exposures to ionizing radiation, there is no evidence or likelihood of increases in congenital malformations that can be attributed to Chornobyl-related radiation.

Method: We determined population rates of neural tube defects, microcephaly and microphthalmia based on 145437 births from 2000 to 2009 in Rivne Province in Ukraine.

Findings: Rivne's rates of neural tube defects, microcephaly and microphthalmia are among the highest in Europe (20, 2.9 and 1.9 per 10.000 live-births respectively). These rates are even higher in a Chornobyl-impacted region of wetlands known as Polisia. The highest NTD rates were noted in areas proximal to two nuclear power plants.

Interpretation: Our findings are sufficiently compelling to warrant further prospective investigations of chronic low dose ionizing radiation impacts on pregnancy outcomes.

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